CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-017
21-018

ADMINISTRATIVE DOCUMENTS

30 **Page(s) Redacted**

DRAFT

LABELING

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 21017/000
Stamp: 22-DEC-1998 Regulatory Due: 22-OCT-1999
Applicant: LILLY
LILLY CORPORATE CENTER
INDIANAPOLIS, IN 46285

Priority: 34S Org Code: 510
Action Goal: District Goal: 23-AUG-1999
Brand Name: HUMALOG MIX 25 (INSULIN LISPRO 25% INJ/I
Established Name:
Generic Name: INSULIN LISPRO 25% INJ/INSULIN LISPRO 75
Dosage Form: INJ (INJECTION)
Strength: 100 U/ML

FDA Contacts: H. RHEE (HFD-510) 301-827-6424 , Project Manager
, Review Chemist
S. MOORE (HFD-510) 301-827-6430 , Team Leader

Overall Recommendation:

ACCEPTABLE on 03-MAR-1999 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment: 1819470
ELI LILLY AND CO
LILLY CORP CTR/WHITE RIVER PK
INDIANAPOLIS, IN 46200

DMF No:
AADA No:

Profile: SVS OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 03-MAR-1999
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: FINISHED DOSAGE MANUFACTURER

Establishment: 9610945
LILLY FRANCE SA
RUE DE COLONEL LILLY B P 10
FEGERSHEIM, , FR

DMF No:
AADA No:

Profile: SVS OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 03-MAR-1999
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: FINISHED DOSAGE MANUFACTURER

APPEARS THIS WAY
ON ORIGINAL

FDA CDER EES
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SUMMARY REPORT

Application: NDA 21018/000
Stamp: 22-DEC-1998 Regulatory Due: 22-OCT-1999
Applicant: LILLY
LILLY CORPORATE CENTER
INDIANAPOLIS, IN 46285

Priority: 3S Org Code: 510
Action Goal: District Goal: 23-AUG-1999
Brand Name: HUMALOG MIX 50 (INSULIN LISPRO 50% INJ/I
Established Name:
Generic Name: INSULIN LISPRO 50% INJ/INSULIN LISPRO 50
Dosage Form: INJ (INJECTION)
Strength: 100 U/ML

FDA Contacts: H. RHEE (HFD-510) 301-827-6424 , Project Manager
, Review Chemist
S. MOORE (HFD-510) 301-827-6430 , Team Leader

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Established Name:
Generic Name: INSULIN LISPRO 50% INJ/INSULIN LISPRO 50
Dosage Form: INJ (INJECTION)
Strength: 100 U/ML

FDA Contacts:
H. RHEE (HFD-510) 301-827-6424 , Project Manager
W. BERLIN (HFD-510) 301-827-6370 , Review Chemist
S. MOORE (HFD-510) 301-827-6430 , Team Leader

Overall Recommendation:

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District Goal: 23-AUG-1999
Applicant: LILLY
LILLY CORPORATE CENTER
INDIANAPOLIS, IN 46285
Brand Name: HUMALOG MIX 25 (INSULIN LISPRO 25% INJ/I
Established Name:
Generic Name: INSULIN LISPRO 25% INJ/INSULIN LISPRO 75
Dosage Form: INJ (INJECTION)
Strength: 100 U/ML

FDA Contacts:			
H. RHEE	(HFD-510)	301-827-6424	, Project Manager
W. BERLIN	(HFD-510)	301-827-6370	, Review Chemist
S. MOORE	(HFD-510)	301-827-6430	, Team Leader

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ON ORIGINAL

CERTIFICATION

NDA Application No.: NDA 21-017

Drug Name: Humalog® Mix25

Pursuant to the provisions of 21 U.S.C. 335a(k)(1), Eli Lilly and Company, through Gregory G. Enas, Ph.D., hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section (a) or (b) [21 U.S.C. 335a(a) or (b)] of the Generic Drug Enforcement Act of 1992, in connection with the above referenced application.

ELI LILLY AND COMPANY

By: Gregory D Enas
Gregory G. Enas, Ph. D.

Title: Director, U.S. Regulatory Affairs

Date: December 21, 1998

CERTIFICATION

NDA Application No.: NDA 21-018

Drug Name: Humalog® Mix50

Pursuant to the provisions of 21 U.S.C. 335a(k)(1), Eli Lilly and Company, through Gregory G. Enas, Ph.D., hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section (a) or (b) [21 U.S.C. 335a(a) or (b)] of the Generic Drug Enforcement Act of 1992, in connection with the above referenced application.

ELI LILLY AND COMPANY

By: Gregory D Enas
Gregory G. Enas, Ph. D.

Title: Director, U.S. Regulatory Affairs

Date: December 21, 1998

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	21017	**Trade Name:**	HUMALOG MIX 25 (INSULIN LISPRO 25% INJ/I
Supplement Number:		**Generic Name:**	INSULIN LISPRO 25% INJ/INSULIN LISPRO 75
Supplement Type:		**Dosage Form:**	Injectable; Injection
Regulatory Action:	AP	**Proposed Indication:**	Treatment of patients with diabetes mellitus for the control of hyperglycemia.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)

____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Does Not Apply
Formulation Status	NO NEW FORMULATION is needed
Studies Needed	
Study Status	

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, JULIE RHEE

/S/ 12-10-99

Signature Date

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	21018	**Trade Name:**	HUMALOG MIX/50 (INSULIN LISPRO 50% INJ/I
Supplement Number:		**Generic Name:**	INSULIN LISPRO 50% INJ/INSULIN LISPRO 50
Supplement Type:		**Dosage Form:**	Injectable; Subcutaneous
Regulatory Action:	AP	**Proposed Indication:**	Treatment of patients with diabetes mellitus for the control of hyperglycemia.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)

____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Does Not Apply
Formulation Status	NO NEW FORMULATION is needed
Studies Needed	No further STUDIES are needed
Study Status	

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, JULIE RHEE

/S/ 12-10-99

Signature Date

RE: NDA #s 21017 and 21018 Insulin Lispro Mixtures and Pediatric Studies

The vast majority of pre-pubescent children with diabetes and many post pubescent teens with diabetes have Type 1 diabetes. The DCCT has shown that long-term complications of Type 1 diabetes can be prevented with intensive insulin therapy. (Subsequent data suggest that intensive therapy can also benefit Type 2 patients.) Fixed ratios of insulin products do not permit frequent dose adjustment and tight control-especially in those without endogenous insulin production. The use of such fixed ratio mixtures cannot be recommended in patients with Type 1 diabetes—especially children. Therefore pediatric studies have not been requested.

/S/
Elizabeth Koller, M.D.
12/17/99

APPEARS THIS WAY
ON ORIGINAL

cc: Orig NDAs 21-017 + 21-018
HFD-510/Div Files 21-017 + 21-018
HFD-510/Koller

APPEARS THIS WAY
ON ORIGINAL

Exclusivity Checklist

NDA: 21-018				
Trade Name: Humalog Mix 50/50				
Generic Name: 50% insulin lispro protamine suspension and 50% insulin lispro (rDNA origin) injection				
Applicant Name: Eli Lilly				
Division: Division of Metabolic and Endocrine Drug products, HFD-510				
Project Manager: Julie Rhee, 7-6424				
Approval Date:				
PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?				
1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.				
a. Is it an original NDA?	Yes	x	No	
b. Is it an effectiveness supplement?	Yes		No	x
c. If yes, what type? (SE1, SE2, etc.)				
Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")	Yes	x	No	
If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.				
Explanation:				
If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:				
Explanation:				
d. Did the applicant request exclusivity?	Yes		No	x
If the answer to (d) is "yes," how many years of exclusivity did the applicant request?				
IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.				
2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?	Yes		No	x
If yes, NDA #				
Drug Name:				
IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS.				
3. Is this drug product or indication a DESI upgrade?	Yes		No	x
IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (even if a study was required for the upgrade).				
PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES				
(Answer either #1 or #2, as appropriate)				
1. Single active ingredient product.	Yes		No	
Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination	Yes		No	x

bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.				
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
Drug Product				
NDA #				
Drug Product				
NDA #				
Drug Product				
NDA #				
2. Combination product.	Yes	x	No	
If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)	Yes	x	No	
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
Drug Product: Humalog				
NDA # 20-563				
Drug Product				
NDA #				
Drug Product				
NDA #				
IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. IF "YES," GO TO PART III.				
PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS				
To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."				
1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.	Yes	x	No	
IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.				
2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been				

sufficient to support approval of the application, without reference to the clinical investigation submitted in the application. For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.				
a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?	Yes	x	No	
If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCKS.				
Basis for conclusion:				
b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?	Yes	x	No	
1) If the answer to 2 b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.	Yes		No	x
If yes, explain:				
2) If the answer to 2 b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?	Yes		No	
If yes, explain:				
c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:				
Investigation #1, Study #: IODK				
Investigation #2, Study #: IODM				
Investigation #3, Study #: IODN				
3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.				
a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")				
Investigation #1	Yes		No	x
Investigation #2	Yes		No	x
Investigation #3	Yes		No	x
If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:				
Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				
b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?				
Investigation #1	Yes		No	x
Investigation #2	Yes		No	x
Investigation #3	Yes		No	x

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:				
Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				
If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):				
Investigation #1	IODK			
Investigation #2	IODM			
Investigation #3	IODN			
4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.				
a. For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?				
Investigation #1		Yes	No	x
IND#:				
Explain: Study conducted outside the U.S.				
Investigation #2		Yes	No	x
IND#:				
Explain: Study conducted outside U.S.				
Investigation #3		Yes	No	x
IND#:				
Explain: Study conducted outside U.S.				
b. For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?				
Investigation #1		Yes	x	No
IND#:				
Explain:				
Investigation #2		Yes	x	No
IND#:				
Explain:				
Investigation #3		Yes	x	No
IND#:				
Explain:				
c. Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)		Yes		No
If yes, explain:				

/S/ 12-9-99
Julie Rhee
Project Manager

/S/ 12-22-99
Solomon Sobel, M.D.
Division Director

cc:OrigNDA
HFD-510/DivFile
HFD-93/Holovac

APPEARS THIS WAY
ON ORIGINAL

Exclusivity Checklist

NDA: 21-017				
Trade Name: Humalog Mix 75/25				
Generic Name: 75% insulin lispro protamine suspension and 25% insulin lispro (rDNA origin) injection				
Applicant Name: Eli Lilly				
Division: Division of Metabolic and Endocrine Drug products, HFD-510				
Project Manager: Julie Rhee (7-6424)				
Approval Date:				
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c. If yes, what type? (SE1, SE2, etc.)				
Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")	Yes	x	No	
If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.				
Explanation:				
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Explanation:				
d. Did the applicant request exclusivity?	Yes		No	x
If the answer to (d) is "yes," how many years of exclusivity did the applicant request?				
IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.				
2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?	Yes		No	x
If yes, NDA #				
Drug Name:				
IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS.				
3. Is this drug product or indication a DESI upgrade?	Yes		No	x
IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (even if a study was required for the upgrade).				
PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES				
(Answer either #1 or #2, as appropriate)				
1. Single active ingredient product.	Yes		No	x
Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination	Yes		No	x

bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.				
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
Drug Product				
NDA #				
Drug Product				
NDA #				
Drug Product				
NDA #				
2. Combination product.	Yes	x	No	
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If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
Drug Product: Humalog				
NDA # 20-563				
Drug Product				
NDA #				
Drug Product				
NDA #				
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1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.	Yes	x	No	
IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.				
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sufficient to support approval of the application, without reference to the clinical investigation submitted in the application. For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.				
a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?	Yes	x	No	
If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCKS.				
Basis for conclusion:				
b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?	Yes	x	No	
1) If the answer to 2 b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.	Yes		No	x
If yes, explain:				
2) If the answer to 2 b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?	Yes		No	
If yes, explain:				
c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:				
Investigation #1, Study #: IODK				
Investigation #2, Study #: IODM				
Investigation #3, Study #: IODN				
3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.				
a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")				
Investigation #1	Yes		No	x
Investigation #2	Yes		No	x
Investigation #3	Yes		No	x
If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:				
Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				
b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?				
Investigation #1	Yes		No	x
Investigation #2	Yes		No	x
Investigation #3	Yes		No	x

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:				
Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				
If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):				
Investigation #1	IODK			
Investigation #2	IODM			
Investigation #3	IODN			
4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.				
a. For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?				
Investigation #1	Yes		No	x
IND#:				
Explain: Study conducted outside the U.S.				
Investigation #2	Yes		No	x
IND#:				
Explain: Study conducted outside the U.S.				
Investigation #3	Yes		No	x
IND#:				
Explain: Study conducted outside the U.S.				
b. For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?				
Investigation #1	Yes	x	No	
IND#:				
Explain:				
Investigation #2	Yes	x	No	
IND#:				
Explain:				
Investigation #3	Yes	x	No	
IND#:				
Explain:				
c. Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)	Yes		No	x
If yes, explain:				

/S/ 12-9-99
Julie Rhee
Project Manager

/S/ 12-29
Solomon Sobel, M.D.
Division Director

cc: Orig NDA
HFD-510/Div File
HFD-93/Mary Ann Holovac

APPEARS THIS WAY
ON ORIGINAL

PATENT INFORMATION

The undersigned declares that the following patents cover the formulation, composition, and/or method of use of Humalog® Mix50™ [50% insulin lispro injection and 50% insulin lispro protamine suspension (r-DNA origin)], as indicated. This product is the subject of this application for which approval is being sought:

Patent No.	Expiration Date	Claim Type
5,461,031	June 16, 2014	formulation, method of use
5,474,978	June 16, 2014	formulation
5,514,646	May 7, 2013	formulation, composition, method of use
5,747,642	June 16, 2014	formulation

The above patents are all owned by or exclusively licensed by Eli Lilly and Company, Indianapolis, Indiana.

EXCLUSIVITY

Eli Lilly and Company (Lilly) does not claim the three-year period of exclusivity for the use of Humalog® Mix50™ [50% insulin lispro injection and 50% insulin lispro protamine suspension (r-DNA origin)] in the treatment of Diabetes Mellitus provided by 21 C.F.R. 314.108 (b)(5).

Gregory G. Enas Date: December 21, 1998

Gregory G. Enas, Ph.D.
Director
U.S. Regulatory Affairs
Eli Lilly and Company

Humalog Mix 75/25

PATENT INFORMATION

The undersigned declares that the following patents cover the formulation, composition, and/or method of use of Humalog® Mix25™ [25% insulin lispro injection and 75% insulin lispro protamine suspension (r-DNA origin)], as indicated. This product is the subject of this application for which approval is being sought:

Patent No.	Expiration Date	Claim Type
5,461,031	June 16, 2014	formulation, method of use
5,474,978	June 16, 2014	formulation
5,514,646	May 7, 2013	formulation, composition, method of use
5,747,642	June 16, 2014	formulation

The above patents are all owned by or exclusively licensed by Eli Lilly and Company, Indianapolis, Indiana.

EXCLUSIVITY

Eli Lilly and Company (Lilly) does not claim the three-year period of exclusivity for the use of Humalog® Mix25™ [25% insulin lispro injection and 75% insulin lispro protamine suspension (r-DNA origin)] in the treatment of Diabetes Mellitus provided by 21 C.F.R. 314.108 (b)(5).

Gregory G Enas

Date: December 21, 1998

Gregory G. Enas, Ph.D.
Director
U.S. Regulatory Affairs
Eli Lilly and Company

APPEARS THIS WAY
ON ORIGINAL